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14. ABSTRACT
Prostate cancer (PCa) is the most common cancer and the second leading cause of cancer death among men in the US. PCa development requires the coordination of many genes and it is expected that simultaneous evaluation of multiple genetic variants can improve the statistical power to detect additional PCa risk variants. We hypothesized that multiple sequence variants in the genome may interact to increase PCa risk. These variants may or may not have known main effect on PCa risk and can be better detected by systematically evaluating gene-gene interactions for SNPs in the genome. We utilized data from the CGEMS study to systematically discover gene-gene interactions in the genome. We also evaluated the gene-gene interactions in two additional independent populations, a population based PCa case-control study from Sweden and a PCa patient population from Johns Hopkins Hospital. We identified 35 pairs of SNPs that significantly interact with the 32 known risk SNPs on PCa risk at a P-value of 1E-05 in the combined analysis of three populations. The most significant interaction detected was between rs12418451 in *MYEOV* and rs784411 in *CEP152*, with a $P_{interaction}$ of 1.15E-07 in the meta-analysis. In addition, we emphasized two pairs of interactions with potential biological implication, including an interaction between rs7127900 near *IGF2/IGF2AS* and rs12628051 in *TNRC6B*, with a P interaction of 3.39E-06; and an interaction between rs7679763 near *TET2* and rs290258 in *SYK*, with a P interaction of 1.49E-06. Those results show statistical evidence for novel loci interacting with known risk-associated SNPs to modify PCa risk. The interacting loci identified provide hints on the underlying molecular mechanism of the associations with PCa risk for the known risk-associated SNPs.

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Table of Contents

INTRODUCTION

Prostate cancer (PCa) is the leading cancer among men in the United States, and is a disease with strong genetic susceptibility. The genetic susceptibility is due to the inheritance of multiple sequence variants, majorly in the form of single nucleotide polymorphisms (SNPs). Most current genetic studies focus only on the single SNP association studies. In contrast, few studies have explored the role of interactions of multiple SNPs with PCa risk, due to limited statistical approaches available to study interactions in a genome-wide level. In fact, gene-gene interaction is the norm rather than exception for complex diseases such as PCa. Inference from tumorigenesis and results from genetic modeling studies suggest that multiple susceptibility genes, either additively or multiplicatively, determine individual risk to PCa. The importance of gene-gene interaction is also supported by empirical evidence from model organisms and human studies. Results from simulation studies suggest that simultaneous evaluation of multiple genetic variants can improve the statistical power to detect additional PCa risk variants and can be more fruitful than traditional approaches that exclusively focus on main effects34. It is expected that additional PCa risk variants will be identified using gene-gene interaction analyses.

In this DOD funded proposal, we propose to 1) identify SNPs in the genome that interact to have stronger effects on PCa risk in the CGEMS GWAS data, 2) confirm the gene-gene interaction effect on PCa risk identified from the CGEMS study in 1,000 PCa cases and 1,000 controls in CAPS, 3) further confirm the gene-gene interaction effects on PCa risk for pairs of SNPs implicated in Aim 2 among the remaining 1,893 cases and 781 controls in CAPS, and 4) fine map the genomic regions where SNPs have been confirmed to have a strong gene-gene interaction effect on PCa risk among all 2,893 cases and 1,781 controls in CAPS.

BODY

Approved Statement of Work:

STATEMENT OF WORK

We will take advantage of two existing large study populations to test this hypothesis. The first study population is the NCI Cancer Genetic Markers of Susceptibility (CGEMS) study, where genome-wide data are available for 1,172 PCa case patients and 1,157 control subjects of European Americans descent. The second study population is our large population-based case-control study from Sweden (CAPS), with 2,893 PCa patients and 1,781 control subjects. These two large study populations are necessary to have sufficient statistical power to detect true interactions in the genome and to remove false positives using a multiple-stage study design.

Aim 1. Identify SNPs in the genome that interact to have stronger effects on PCa risk in the CGEMS GWAS data.

Step by step method and expected results

1) **(Months 1)** Preparation of the study, including IRB and other logistic issues.
2) **(Months 2)** Pre-association analysis and imputation of all the SNPs in the genome.
3) **(Months 3-12)** Logistic regression analysis to identify pairs of SNPs that interact to have stronger effects on PCa risk.

4) **(Months 3-12)** Bayesian epistasis association mapping (BEAM) to identify pairs of SNPs that interact to have stronger effects on PCa risk.

Outcome and deliverables

We will identify pairs of SNPs in the genome whose interaction terms reach $P < 0.001$. Based on the results of genome-wide searches for SNPs that interact with rs1447295 at 8q24, we expect to identify ~450 independent SNPs that interact with each of the twelve known PCa risk SNPs. In addition, we expect to identify additional SNPs that have stronger two-way or three-way interaction effects on PCa risk from the BEAM analysis. These SNPs, estimated to number around ~5,000, will be selected for further confirmation in Aim 2.

Aim 2. Confirm gene-gene interaction effects on PCa risk identified from the CGEMS study in 1,000 PCa cases and 1,000 controls in CAPS

Step by step method and expected results

1) **(Months 6-16)** Genotype ~5,000 SNPs among 1,000 cases and 1,000 controls in CAPS using iSELECT of Illumina.
2) **(Months 17-20)** Analyze data using logistic regression and BEAM methods to remove false positives identified in Aim 1 and obtain a smaller subset of SNPs that most likely represent true interaction for further confirmation in larger samples.

Outcome and deliverables

Most of the false positive interactions will be removed from this aim. We expect 125 pairs of SNPs in this stage will have $P < 0.05$ and have the same direction of interaction effect as in the CGEMS data [(5,000 x 0.05)/2]. These SNPs will be selected for further confirmation in Aim 3. The actual number of SNPs may be higher if there are more true interaction effects in the genome.

Aim 3. Further confirm the gene-gene interaction effects on PCa risk for pairs of SNPs implicated in Aim 2 among the remaining 1,893 cases and 781 controls in CAPS

Step by step method and expected results

1) **(Months 21-24)** Genotype 125 SNPs among 1,893 cases and 781 controls in CAPS using iPLEX of Sequenom.
2) **(Months 25-28)** Analyze data using logistic regression and BEAM methods to remove false positives identified in Aim 1 and obtain a smaller subset of SNPs that most likely represents true interaction for further confirmation in larger samples.

Outcome and deliverables

We will use a stringent genome-wide significance level from the joint analysis ($P < 10^{-8}$) to declare significant interaction. In fact, considering that 12 genome-wide associations were performed, it is more conservative to use the cutoff of $P < 10^{-9}$. The actual number of SNPs whose interactions meet the criteria depends on the number of true interactions in the genome with the OR detectable in our study.

Aim 4. Fine map the genomic regions where SNPs have been confirmed to have strong gene-gene interaction effect on PCa risk among all 2,893 cases and 1,781 controls in CAPS

Step by step method and expected results

1) **(Months 29-30)** Functional SNPs and tagging SNPs will be selected in the genomic region for each of the SNPs implicated in Aim 3.
2) **(Months 29-30)** Selected SNPs will be genotyped in 2,893 cases and 1,781 controls of CAPS using iPLEX of Sequenom.
3) **(Months 31-36)** Fine mapping data analysis will be performed to identify the most strongly associated SNPs (interaction effect) in each of the regions implicated in Aim 3.

Summary report

By July 2012, we will be in the 36th month of this funded project. During the last year, we have completed the following 1) performed a genome-wide epistasis analysis of the 32 risk SNPs reported in CAPS population 2) performed a genome-wide epistasis analysis of the 32 risk SNPs reported in JHH population 3) performed a meta-analysis and fine-mapping studies of the three GWAS populations to identify interaction effect in a combined samples of 4,723 PCa cases and 4,792 controls.

Detailed report

Study design modification. In our initial report, we proposed to conduct a genome-wide search in the CGEMS population and follow the top hits in an additional two study populations (CAPS and JHH). During year 3, we were able to obtain access to the GWAS data for the CAPS and JHH populations. Therefore, we also conducted a genome-wide search for SNPs that interact with the 32 risk SNPs using CAPS and JHH populations. We also performed a meta-analysis and a fine-mapping study based on the GWAS data of the three populations. Compared with our original study design, the new design greatly improved our statistical power to detect SNP-SNP interactions. For example, we were only able to detect a relatively large effect (OR>1.7) based on our initial design of using 1,176 cases and 1,101 controls from the CGEMS study. However, we were able to detect a modest to large effect of interaction (OR>1.3) using a total of 4,723 PCa cases and 4,792 controls based on three GWAS populations.

Study populations. The first population was obtained from Stage 1 of the National Cancer Institute Cancer Genetic Markers of Susceptibility (CGEMS) study. It included 1,176 PCa cases and 1,101 control subjects, selected from the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial. The genotype and phenotype data of the study are publicly available and our use of the data was approved by CGEMS.

The second GWAS population included 1,583 prostate cancer patients and 519 control subjects that matched the age distribution of case subjects from CAPS, a population-based PCa case-control study from Sweden (CAPS). Briefly, the CAPS population was recruited from four regional cancer registries in Sweden and diagnosed between July 2001 and October 2003. The clinical characteristics of these patients are presented in Supplementary Table 1.

The third population was from a Johns Hopkins Hospital (JHH) PCa GWAS which included 1,964 PCa cases and 3,172 control subjects. The cases are Caucasian PCa patients who underwent radical prostatectomy for the treatment of PCa at JHH from January 1, 1999, through December 31,

2008 [1]. The clinical characteristics of these patients are presented in Supplementary Table 2. The control subjects for this population were an independent group of Caucasian individuals from the Illumina iControlDB (iControls) dataset (https://www.illumina.com/science/icontrodb.ilmn).

Genotype data, imputation, and quality control. GWAS of the CAPS population was performed using Affymetrix 5.0 chip. GWAS of the JHH case population was performed using the Illumina 610K chip. GWAS of the iControls population was performed using Illumina Hap300 and Hap550 Chips. GWAS of the CGEMS population was performed using HumanHap300 and HumanHap240 assays from Illumina Corp.

For each GWAS population, we imputed all the known SNPs that are catalogued in HapMap Phase II (www.hapmap.org) using the IMPUTE computer program [2] with a posterior probability of 0.9 as a threshold to call genotypes. Individuals with a call rate below 0.95 were removed from GWAS analysis. The following quality control criteria were used to filter SNPs: MAF < 0.01, HWE < 0.001 and call rate < 0.95.

Prostate cancer known risk SNPs identified from GWAS. The 33 PCa known risk-associated SNPs were discovered by GWAS and the following fine-mapping studies, with *P*- values equal or smaller than of 10E-7 [3-17]. The detailed information for the 33 risk SNPs are presented in Table 1. The SNP rs16901979 was not evaluated in the following interaction analysis due to the unavailability of imputation of this SNP since it was not catalogued in the HapMap database.

Statistical analysis. Multiplicative interactions between each one of the 32 known PCa risk variants and each SNP in the genome were systematically tested by including both SNPs and an interaction term (product of two SNPs), as implemented in the computer program PLINK[18]. Ancestral proportions obtained based on EIGENSOFT software [19]were included as covariates to minimize the impact of potential population stratification in the JHH population. An additive genetic model was used, where the genotypes were coded as 0,1, and 2 and each SNP was treated as a continuous variable. The interaction term was tested using a Wald test, with degree of freedom of 1. A meta-analysis of the interaction term for the three study populations was performed using the method developed by Manning et al [20] . Briefly, the meta-OR (OR_M) of the interaction term across the three populations was estimated using an inverse-variance weighted meta-analysis where

$$\ln(OR_M) = \sum_{i=1}^{3}(w_i \ln(OR_i)/\sum_{i=1}^{3} w_i),\ w_i = 1/\mathrm{var}(\ln(OR_i))$$ and

$$se(\ln(OR_M)) = [\sum_{i=1}^{3}(1/\mathrm{var}(\ln(OR_i))]^{-1/2}.$$(20)

Results

After imputation and applying quality control (QC) criteria, 1,314,700, 1,646,196, and 1,757,946 SNPs remained for CAPS, JHH, and CGEMS studies, respectively. A total of 1,117,531 common SNPs for those three populations were used in the interaction analysis.

We examined the inflation factor and the quantile-quantile plots for interaction tests in the combined analysis of three populations. No systematic bias was observed, as the inflation factors for the 32 GWAS scans for SNP-SNP interactions ranged from 0.98 to 1.03 (Supplementary Table 3).

The results for the top ranked SNPs that interacted with each of the 32 known PCa-risk SNPs ($P_{interaction}$ <1.0E-05 in the meta-analysis) were presented in Supplementary Table 4. For SNPs in linkage disequilibrium (LD) (as defined by r2>0.5), only the one with the smallest *P* -value based on

meta-analysis was included in the Supplementary Table 4. We then further examined the interaction effects for the top ranked SNPs ($P_{interaction}$ <1E-05*)* in each of the three populations. SNPs that significantly interacted with the 32 SNPs in all three populations at a nominal $P_{interaction}$ of 0.05 were presented in Table 2. No SNP-SNP interaction reached a genome-wide significant level of 1.5E-09 (0.05/(1e+6*32). The most significant interaction was observed between rs12418451 in the *MYEOV* gene region and rs784411 in the intron of *CEP152*, with a $P_{interaction}$ of 1.15E-07 ($OR_{interaction}$= 1.42; 95% CI: 1.25-1.61) in the meta-analysis. This interaction pair was significant in all three populations and the effects of the interaction were in the same direction ($P_{interaction}$ = 0.008*,* $OR_{interaction}$ **=**1.55 (95% CI: 1.12-2.16) for CAPS; $P_{interaction}$ = 0.005, $OR_{interaction}$ = 1.34 (95% CI: 1.14-1.58) for JHH; and $P_{interaction}$ = 0.001, $OR_{interaction}$ = 1.53 (95% CI = 1.18-1.99) in CGEMS, respectively) (Table 2).

Among the other 34 pairs of interactions that were significant at a $P_{interaction}$ cutoff of 1E-05 in the meta-analysis, two pairs were noteworthy to be emphasized when considering possible biological function. The first pair involved an interaction between rs7127900 at *IGF2/IGF2AS* region and rs12628051 in the intron of *TNRC6B*, with a $P_{interaction}$ of 3.39E-06 ($OR_{interaction}$ = 1.30, 95% CI = 1.17-1.46) (Table 2). The interaction was significant in all three populations and the effects of the interaction were in the same direction ($P_{interaction}$ = 0.002, OR $_{interaction}$= 1.50, 95 % CI = 1.16-1.93 in CAPS; $P_{interaction}$ = 0.006, $OR_{interaction}$ = 1.24, 95 % CI = 1.06-1.44 in JHH; $P_{interaction}$ = 0.014, $OR_{interaction}$ = 1.32, 95 % CI = 1.06-1.65 in CGEMS). The 2nd pair of interaction was between rs7679763 in *TET2* gene region and rs290258 in the promoter region of SYK, with a $P_{interaction}$ of 1.49E-06 (OR = 0.75, 95% CI = 0.67-0.84) (Table 2). Similarly, the interaction effect was consistently observed in all three populations with the same direction of interaction effect ($P_{interaction}$ = 0.002, $OR_{interaction}$ = 0.66, 95 % CI = 0.51-0.86 in CAPS; $P_{interaction}$ = 0.003, OR $_{interaction}$= 0.78, 95 % CI = 0.67-0.92 in JHH; $P_{interaction}$ = 0.014, $OR_{interaction}$ = 0.75, 95 % CI = 0.59-0.94 in CGEMS).

Discussion

To our knowledge, our study represents one of the first comprehensive gene-gene interaction scans in three PCa GWAS populations. Specifically, we performed a genome-wide gene-gene interaction scan for each of the 32 known prostate cancer risk-associated variants identified from genome-wide association studies in three case-control populations of European descents, which includes a total of 4,723 PCa cases and 4,792 controls. In the meta-analysis, we found 35 pairs of SNP-SNP interactions that were significantly associated with PCa risk ($P_{interaction}$ <1E-05). In addition, the interactions for those 35 pairs were significant in all three populations (all $P_{interaction}$ <0.05). Among those 35 pairs of statistically significant interactions, we emphasized three pairs of interactions with potential biological implication, including an interaction between rs12418451 in *MYEOV* and rs16961635 in *CEP152*, with a $P_{interaction}$ of 1.15E-07 (OR = 1.42, 95 % CI = 1.25-1.61), an interaction between rs7127900 at *IGF2/IGF2AS* region and rs12628051 in the intron of *TNRC6B*, with a $P_{interaction}$ of 3.39E-06 (OR = 1.30, 95% CI = 1.17-1.46), an interaction between rs7679763 in *TET2* gene region and rs290258 in the promoter region of SYK, with a $P_{interaction}$ of 1.49E-06 (OR = 0.75, 95% CI = 0.67-0.84).

The discovery of approximately three dozen PCa risk variants using single SNP analysis suggests that it is possible to detect individual risk variants. However, when the underlying genetic model involves interaction of multiple genes, a single gene approach is less effective and may not be able to explain the complex etiology of the disease. Therefore, evaluation of the joint effect (epistasis) of multiple genetic variants is critical to understand the underlying causes of complex diseases [21], especially in the situation where several individual risk variants have been identified. The next question is to explore whether other SNPs interact with those SNPs to modify risk to PCa. The

identified loci that interact with the known PCa risk-associated SNPs may help to elucidate the underlying molecular mechanisms of the associations of those risk SNPs.

The most significant interaction was seen between the PCa risk-associated SNPS rs12418451 and rs784411. The SNP rs12418451 is located at the 11q13.2 that is ~77kb upstream of *TPCN2*, a putative cation-selective ion channel gene, and ~126kb upstream of *MYEOV*, an oncogene that has been implicated in multiple cancers [22-26]. The SNP rs784411 resides in the intron of CEP152, a centrosomal protein that was recently shown to function as a regulator of genomic integrity [27] and cellular response to DNA damage[28]. Given the limited information, we speculate that observed interaction may reflect the close collaboration of MYEOV (or TPCN2, even though it is less likely) and CEP152 in the same or different oncogenic pathways that drive the tumorigenesis of prostatic epithelial cells.

Among the two SNPs that were shown to consistently interact with the PCa risk-associated SNP rs7127900 at 11p15.5, one SNP (rs12628051) is located within TNRC6B, which encodes a RNA interference (RNAi) machinery component protein crucial for the miRNA/siRNA-dependent translational repression or degradation of target mRNAs. It is worthy to mention that this gene also contains a GWAS-identified PCa risk-associated SNP (rs9623117). Several mechanisms may potentially explain for these interactions. Firstly, we noticed that at ~70 kb telomeric to rs7127900 reside the PCa-implicated *IGF2* gene and its antisense transcript-encoding *IGF2AS*. IGF2 encodes a member of the insulin family of polypeptide growth factors that promotes cell proliferation during fetal development but becomes less active in healthy adults due to genomic imprinting. Dysregulated overexpression of IGF2 caused by loss of imprinting (LOI) has been associated with a variety of human cancers including PCa [29-32]. IGF2AS encodes a predictably non-coding RNA that is antisense to IGF2 and thus may potentially regulate IGF2 expression through RNAi in a similar manner as some other natural antisense transcripts. Thus one plausible scenario is that TNRC6B may affect the RNAi-mediated transcriptional regulation of IGF2AS on IGF2, which may underlie the observed interaction between genetic variants within these two loci. Secondly, there are two microRNA (miRNA) genes located at 11p15.5, miR-4686 (~40kb from the PCa-risk SNP rs7127900) and miR-483 (~80kb from rs7127900). Although the role of miR-4686 remains to be determined, miR-483 has been demonstrated to act as an oncogene to suppress proapoptotic BBC3 (PUMA) or tumor suppressive DPC4(Smad4) in a variety of human cancers[33,34]. Thus an alternative mechanism for the observed interaction between the 11p15.5 locus and the TNRC6B locus is that genetic variants in TNRC6B may affect the miR-483 (or miR4686)-mediated RNAi toward its/their target tumor suppressor genes.

Another pair of interacting SNPs were found between rs7679673 (~ 6kb upstream of *TET2*) and rs290258 (~8kb upstream of *SYK*). TET2 encodes an enzyme hydroxylating methylcytosine and is implicated in epigenetic programming that involves DNA methylation and demethylation (Reviewed in [35]). The critical role of TET2 in cancer is suggested by the observation that loss of function mutations of TET2 are frequently identified in various hematologic malignancies[36,37]. As a non-receptor Tyrosine protein kinase that mediates cellular proliferation and differentiation, SYK is believed to function as a potential tumor suppressive gene (reviewed in [38]. It is noteworthy that hypermethylation of SYK gene promoter has been frequently found in and widely associated with lung, gastric, and breast cancer [39,40]. Thus although it remains to be determined whether SYK promoter in prostatic tumors also undergoes silencing via DNA methylation, the observed interaction between TET2 and SYK suggests that it is a plausible hypothesis.

Two SNPs (rs731174 and rs10812303) were found to interact with the GWAS-identified PCa risk-associated SNP rs4430796, residing within *HNF1B*, a homeodomain-containing transcription factor

whose expression alteration has been widely implicated in various human cancers including PCa. The SNP rs731174 is located within the intron of *EPHA10*, a member of the EPH subfamily of receptor tyrosine kinases (RTKs). This family of RTKs play an important role in cell-cell communication regulating cell attachment, shape, and mobility in epithelial cells and are believed to be implicated in carcinogenesis (reviewed in [41]. It is possible that HNF1Ba and EPHA10 collaborate in the signaling network that is crucial for the well-being of prostatic cells whereas the genetic variants located within these two genes may synergistically contribute to the oncogenesis of PCa. The other SNP rs10812303 is ~40kb upstream of *TUSC1*, an intronless gene that has been suggested to serve as a tumor suppressor in lung tumorigenesis [42].Thus the interaction between genetic variants in TUSC1 and HNF1B may also suggest a plausible collaboration of these two genes.

In summary, our systematic evaluation of gene-gene interactions in three GWAS populations suggested a list of loci interacting with known PCa risk-associated SNPs that may warrant follow-up in other study populations. Three pairs of interactions are worthwhile to be emphasized, including an interaction between rs12418451 in the *MYEOV* gene region and rs784411 in the intron of *CEP152*, an interaction between rs7127900 in the *IGF2/IGF2AS* gene region and rs12628051 in the intron of *TNRC6B*, and an interaction between rs7679673 in the *TET2* gene region and rs290258 in the intron of *SYK.* Those results showed statistical evidence for genes interacting with known risk-associated SNPs on PCa risk. The interacting loci identified also provide more hints on the underlying molecular mechanism of the associations with PCa risk for the known risk-associated SNPs.

While we have made great progress to complete the original aims, we received approval from DOD to perform additional gene-gene interaction analysis based on several novel statistical approaches developed recently, which were not originally proposed in the study. In addition, we also propose to perform bioinformatics analysis on the pairs of SNP-SNP interactions we identified. The additional statistical and bioinformatics analysis will help to identify additional novel SNP pairs that confer risk to prostate cancer, and will facilitate to pinpoint the potential biological mechanisms underlying the gene-gene interactions we identified and prostate cancer risk.

KEY RESEARCH ACCOMPLISHMENTS

1) Completed a genome-wide search for SNPs interacting with the 32 risk SNPs in the CAPS population
2) Completed a genome-wide search for SNPs interacting with the 32 risk SNPs in the JHH population
3) Completed a meta-analysis and a fine-mapping study of the three GWAS populations (comprised of 4,723 PCa cases and 4,792 controls) to identify SNPs interacting with the 32 risk SNPs

REPORTABLE OUTCOMES

1) Thirty-five pairs of SNP-SNP interactions were significantly associated with PCa risk (a $P_{interaction}$ < 1E-05) in the meta-analysis. In addition, the interaction for those 35 pairs was significant in all three populations (all $P_{interaction}$ < 0.05 in CGEMS, JHH, and CAPS) (see Table 1).

2) The most significant interaction was detected between rs12418451 in *MYEOV* and rs784411 in *CEP152*, with a $P_{interaction}$ of 1.15E-07 in the meta-analysis of three populations (Table 1).
3) Two more pairs of interactions that were significant at a $P_{interaction}$ < of 1E-05 in the meta-analysis were biologically interesting, including an interaction between rs7127900 at *IGF2/IGF2AS* region and rs12628051 in the intron of *TNRC6B*, with a $P_{interaction}$ of 3.39E-06 (OR = 1.30, 95% CI = 1.17-1.46), and an interaction between rs7679763 in *TET2* gene region and rs290258 in the promoter region of SYK, with a $P_{interaction}$ of 1.49E-06 (OR = 0.75, 95% CI = 0.67-0.84).

CONCLUSION

1) We have made great progress in achieving the goals described in the approved statement of work.
2) We have identified and confirmed SNPs in the genome that significantly interacts with the 32 known PCa risk SNPs in three of our study populations.
3) The interacting loci identified provide more hints on the underlying molecular mechanism of the associations with PCa risk for the known risk-associated SNPs.
4) We are still working on the additional analysis that we proposed for the approved no-cost extension period.

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Table 1. Reported SNPs associated with Prostate Cancer

CHR	SNPs	Cytogenetic bands	Position	Known genes	m/M allele	Risk allele
2	rs1465618	2p21	43,407,453	*THADA*	A/G	A
2	rs721048	2p15	62,985,235	*EHBP1*	A/G	A
2	rs12621278	2q31.1	173,019,799	*ITGA6*	G/A	A
3	rs2660753	3p12	87,193,364	--	T/C	T
3	rs10934853	3q21.3	129,521,063	*EEFSEC*	A/C	A
4	rs17021918	4q22.3	95,781,900	*PDLIM5*	T/C	C
4	rs7679673	4q24	106,280,983	*TET2*	A/C	C
6	rs9364554	6q25	160,753,654	*SLC22A3*	T/C	T
7	rs10486567	7p15	27,943,088	*JAZF1*	A/G	G
7	rs6465657	7q21	97,654,263	*LMTK2*	T/C	C
8	rs2928679	8p21.2	23,494,920	*SLC25A37*	A/G	A
8	rs1512268	8p21.2	23,582,408	*NKX3.1*	T/C	T
8	rs10086908	8q24 (5)	128,081,119	--	C/T	T
8	rs16901979	8q24 (2)	128,194,098	--	A/C	A
8	rs16902094	8q24.21	128,389,528	--	N/A	G
8	rs620861	8q24 (4)	128,404,855	--	A/G	G
8	rs6983267	8q24 (3)	128,482,487	--	G/T	G
8	rs1447295	8q24 (1)	128,554,220	--	A/C	A
9	rs1571801	9q33	123,467,194	*DAB2IC*	G/A	A
10	rs10993994	10q11	51,219,502	*MSMB*	T/C	T
10	rs4962416	10q26	126,686,862	*CTBP2*	C/T	C
11	rs7127900	11p15.5	2,190,150	*IGF2, IGF2AS, INS, TH*	G/A	A
11	rs12418451	11q13 (2)	68,691,995	--	A/G	A
11	rs10896449	11q13 (1)	68,751,243	*MYEOV*	A/G	G
17	rs11649743	17q12 (2)	33,149,092	*HNF1B*	A/G	G
17	rs4430796	17q12 (1)	33,172,153	*HNF1B*	A/G	A
17	rs1859962	17q24.3	66,620,348	--	G/T	G
19	rs8102476	19q13.2	43,427,453	*PPP1R14A*	T/C	C
19	rs887391	19q13	46,677,464	--	C/T	T
19	rs2735839	19q13	56,056,435	*KLK3*	A/G	G
22	rs9623117	New 22q13	38,782,065	*TNRC6B*	C/T	C
22	rs5759167	New 22q13.2	41,830,156	*TTLL1,* ***BIK****, MCAT, PACSIN2*	T/G	G
23	rs5945619	Xp11	51,258,412	*NUDT10,* ***NUDT11****, LOC340602*	C/T	C

Abbreviation: Chr, chromosome; BP: Base pair position is based on NCBI build 36. m/M denotes minor allele/ major allele.

Table 2. Results for top SNPs that interact with the known PCa-risk SNPs ($P_{interaction}$ <1.0E-05 in the meta-analysis, and $P_{interaction}$ <0.05 in each of the three populations)

SNP 1			SNP 2							Meta- results		CAPS		JHH		CGEMS	
CHR	SNP	Gene	CHR	SNP		Minor Allele	Gene	Location	Relative Position	P	OR	P	OR	P	OR	P	OR
2	rs1465618	*THADA*	4	rs11735008	393,303	G	*ABCA11P*	Intergenic	15,921	6.65E-06	0.76(0.68-0.86)	5.04E-03	0.69(0.54-0.90)	3.11E-02	0.83(0.71-0.98)	1.35E-03	0.69(0.55-0.86)
			13	rs9567349	43,535,405	G	*NCRNA00284*	Intergenic	32,806	3.93E-06	0.61(0.49-0.75)	4.57E-04	0.41(0.25-0.67)	3.24E-02	0.72(0.54-0.97)	3.97E-03	0.57(0.39-0.84)
3	rs10934853	*EEFSEC*	9	rs7847271	116,870,633	A	*TNC*	Intron		3.85E-06	0.67(0.56-0.79)	7.73E-03	0.60(0.41-0.87)	2.56E-03	0.68(0.54-0.88)	1.87E-02	0.69(0.50-0.94)
			18	rs998124	40,979,660	G	*MIR4319*	Intergenic	-175,531	5.21E-06	1.33(1.18-1.51)	3.56E-02	1.39(1.02-1.88)	3.64E-03	1.28(1.08-1.51)	3.56E-03	1.42(1.12-1.80)
4	rs17021918	*PDLIM5*	3	rs9757252	86,977,168	T	*VGLL3*	Intergenic	92,645	4.73E-06	1.25(1.13-1.37)	8.45E-03	1.35(1.08-1.69)	2.23E-03	1.22(1.07-1.38)	2.16E-02	1.24(1.03-1.50)
4	rs7679673	*TET2*	9	rs290258	92,595,560	G	*SYK*	Intergenic	-8,273	1.49E-06	0.75(0.67-0.84)	2.11E-03	0.66(0.51-0.86)	3.01E-03	0.78(0.67-0.92)	1.39E-02	0.75(0.59-0.94)
			22	rs5751168	21,175,240	T	*ZNF280B*	Intron		4.11E-06	1.44(1.23-1.67)	4.75E-05	2.19(1.50-3.19)	3.38E-02	1.25(1.02-1.53)	9.09E-03	1.48(1.10-1.99)
7	rs10486567	*JAZF1*	3	rs1795355	41,574,530	T	*ULK4*	Intron		9.46E-06	0.79(0.71-0.88)	3.37E-02	0.77(0.60-0.98)	9.11E-03	0.83(0.72-0.95)	2.14E-03	0.73(0.60-0.89)
			3	rs11720607	174,325,971	G	*SPATA16*	Intron		4.87E-06	0.73(0.63-0.83)	2.45E-03	0.62(0.45-0.84)	2.34E-03	0.75(0.62-0.90)	5.43E-02	0.77(0.58-1.00)
7	rs6465657	*LMTK2*	16	rs8057939	47,951,777	C	*C16orf78*	Intergenic	-13,532	4.71E-06	1.37(1.20-1.57)	3.31E-02	1.43(1.03-1.98)	1.03E-03	1.36(1.13-1.63)	1.70E-02	1.36(1.06-1.75)
8	rs10086908		6	rs10456809	17,921,804	T	*KIF13A*	Intron		4.83E-06	1.25(1.14-1.38)	1.30E-02	1.31(1.06-1.62)	2.28E-03	1.23(1.08-1.40)	1.69E-02	1.26(1.04-1.52)
8	rs1447295	*NA*	7	rs7789197	40,931,652	A	*INHBA*	Intergenic	763,474	3.36E-06	0.66(0.56-0.79)	2.57E-03	0.55(0.38-0.81)	7.27E-03	0.72(0.56-0.91)	1.06E-02	0.66(0.48-0.91)
			9	rs12682851	8,002,418	G	*C9orf123*	Intergenic	-212,619	1.53E-06	0.72(0.63-0.82)	9.66E-03	0.67(0.50-0.91)	2.15E-03	0.75(0.62-0.90)	6.56E-03	0.70(0.54-0.90)
			10	rs10885582	116,317,540	T	*ABLIM1*	Intron		3.70E-06	0.73(0.63-0.83)	9.33E-05	0.54(0.39-0.73)	1.27E-02	0.79(0.66-0.95)	3.46E-02	0.75(0.57-0.98)
8	rs6983267	*NA*	6	rs1011119	19,972,144	G	*ID4*	Intergenic	23,250	7.20E-06	0.81(0.74-0.89)	1.45E-02	0.76(0.61-0.95)	2.85E-03	0.83(0.74-0.94)	1.58E-02	0.80(0.67-0.96)
9	rs1571801	*DAB2IC*	8	rs2219968	79,119,213	A	*PKIA*	Intergenic	-471,678	6.07E-07	1.30(1.17-1.43)	1.18E-02	1.35(1.07-1.70)	1.64E-04	1.30(1.14-1.50)	3.17E-02	1.24(1.02-1.52)
			8	rs13264970	83,236,384	C	*SNX16*	Intergenic	-319,308	3.53E-06	0.77(0.69-0.86)	1.50E-02	0.74(0.59-0.94)	5.02E-03	0.80(0.68-0.93)	3.92E-03	0.72(0.58-0.90)
			10	rs1547851	92,364,806	T	*HTR7*	Intergenic	125,750	7.45E-06	1.59(1.30-1.95)	2.72E-03	1.98(1.27-3.09)	7.35E-03	1.49(1.11-1.99)	2.42E-02	1.52(1.06-2.20)
10	rs4962416	*CTBP2*	5	rs10940579	57,166,575	C	*ACTBL2*	Intergenic	-352,182	3.81E-06	1.32(1.18-1.49)	4.85E-02	1.36(1.00-1.84)	1.77E-03	1.29(1.10-1.51)	4.74E-03	1.39(1.10-1.74)
11	rs10896449	*MYEOV*	12	rs17354197	88,169,501	T	*DUSP6*	Intergenic	96,467	8.82E-06	1.41(1.21-1.64)	3.97E-02	1.49(1.02-2.18)	2.35E-03	1.37(1.12-1.67)	1.10E-02	1.45(1.09-1.92)
11	rs12418451	*MYEOV*	3	rs10513723	176,062,702	A	*NAALADL2*	Intron		5.61E-06	1.41(1.21-1.63)	7.22E-03	1.58(1.13-2.21)	1.61E-02	1.27(1.05-1.54)	1.46E-03	1.64(1.21-2.22)
			8	rs7829048	4,689,690	C	*CSMD1*	Intron		9.76E-06	0.74(0.65-0.85)	1.22E-02	0.68(0.50-0.92)	4.52E-02	0.84(0.71-1.00)	1.81E-04	0.60(0.46-0.78)
			15	rs784411	46,827,089	C	*CEP152*	Intron		1.15E-07	1.42(1.25-1.61)	8.83E-03	1.55(1.12-2.16)	5.28E-04	1.34(1.14-1.58)	1.32E-03	1.53(1.18-1.99)
11	rs7127900	IGF2, IGF2AS	8	rs13258681	124,783,903	C	*ANXA13*	Intron		3.65E-06	1.32(1.17-1.48)	4.58E-02	1.32(1.01-1.73)	5.43E-04	1.33(1.13-1.56)	1.90E-02	1.31(1.05-1.64)
		INS,TH	22	rs12628051	38,984,222	C	*TNRC6B*	Intron		3.39E-06	1.30(1.17-1.46)	1.82E-03	1.50(1.16-1.93)	6.14E-03	1.24(1.06-1.44)	1.44E-02	1.32(1.06-1.65)
17	rs4430796	*HNF1B*	1	rs731174	37,969,428	C	*EPHA10*	Intron		4.55E-06	1.27(1.15-1.40)	5.03E-02	1.24(1.00-1.54)	3.20E-02	1.18(1.01-1.38)	1.13E-04	1.41(1.19-1.68)
			2	rs12694942	158,518,681	T	*UPP2*	Intergenic	-41,256	7.84E-06	0.80(0.73-0.88)	5.22E-03	0.75(0.61-0.92)	1.87E-03	0.79(0.68-0.92)	6.36E-02	0.85(0.72-1.01)
			9	rs10812303	25,712,117	T	*TUSC1*	Intergenic	-43,261	5.59E-06	1.34(1.18-1.52)	6.63E-03	1.46(1.11-1.91)	7.57E-03	1.27(1.07-1.52)	9.01E-03	1.37(1.08-1.73)
17	rs1859962	*NA*	2	rs16867225	180,749,531	A	*CWC22*	Intergenic	-169,506	3.12E-06	0.64(0.53-0.77)	1.33E-03	0.48(0.30-0.75)	4.80E-03	0.70(0.54-0.90)	1.84E-02	0.65(0.45-0.93)
			7	rs10277209	108,790,810	C	*C7orf66*	Intergenic	-478,937	3.81E-06	1.36(1.19-1.55)	4.08E-02	1.39(1.01-1.89)	4.04E-03	1.29(1.08-1.53)	1.55E-03	1.52(1.17-1.97)

19	rs2735839	*KLK3*	20	rs6089829	61,139,481	A	*LOC63930*	Intron		3.21E-06	0.74(0.65-0.84)	2.53E-02	0.71(0.52-0.96)	1.26E-03	0.75(0.64-0.90)	1.10E-02	0.72(0.56-0.93)
19	rs8102476	*PPP1R14A*	1	rs1866967	29,958,249	G	*PTPRU*	Intergenic	432,337	5.16E-06	0.82(0.75-0.89)	2.70E-02	0.79(0.64-0.97)	5.10E-03	0.85(0.75-0.95)	2.97E-03	0.78(0.66-0.92)
19	rs887391	*NA*	4	rs735172	5,809,770	C	*EVC*	Intron		2.03E-06	1.31(1.17-1.46)	6.58E-03	1.43(1.10-1.85)	2.37E-03	1.27(1.09-1.47)	1.02E-02	1.32(1.07-1.63)
			5	rs4463179	13,558,432	A	*DNAH5*	Intergenic	185,005	2.22E-06	0.64(0.53-0.77)	3.00E-02	0.64(0.42-0.96)	8.35E-05	0.59(0.46-0.77)	8.28E-02	0.73(0.51-1.04)
22	rs9623117	*TNRC6B*	4	rs1713511	43,472,127	A	*KCTD8*	Intergenic	398,550	7.87E-06	1.31(1.16-1.47)	4.94E-03	1.54(1.14-2.09)	6.71E-03	1.23(1.06-1.44)	1.06E-02	1.36(1.07-1.72)

Abbreviations: SNP1 indicate the 32 known PCa-risk SNPs. SNP 2 indicates the interacting SNPs; Chr, chromosome; Relative position is the distance of SNP2 relative to the nearest gene if SNP2 is located in the intergenic region; OR : Odds Ratio; P and OR are for the multiplicative interaction term. P and OR for the Meta-analysis are calculated based on a Cochran-Mantel-Haenszel test. CAPS: PCa case-control study from Sweden; JHH: Johns Hopkins Hospital; CGEMS: the Cancer Genetic Markers of Susceptibility;

Supplementary Table 1. Clinical and demographic characteristics of subjects in CAPS

Characteristics	# (%) of cases			# (%) of
	Aggressive (N=686)	Localized (N=795)	All cases (N=1483)	controls (N=519)
Age at enrollment (Year)				
Mean (sd)	67.91(7.25)	64.59(6.55)	66.13(7.07)	67.24(7.35)
Age at disgnosis				
≤ 65	60.24(3.76)	59.55(3.66)	59.81(3.71)	NA
> 65	72.5(4.35)	70.5(4.15)	71.6(4.38)	NA
Family History (first-degree relatives)				
No	569(82.94)	623(78.36)	1192(80.38)	466(89.79)
Yes	117(17.06)	172(21.64)	289(19.49)	53(10.21)
Missing data	0(0)	0(0)	2(.13)	0(0)
PSA levels at diagnosis for cases or at enrollment for controls (ng/ml)				
≤ 4	20(2.92)	98(12.33)	118(7.96)	413(79.58)
4-9.99	94(13.70)	430(54.08)	524(35.33)	81(15.61)
10-19.99	117(17.06)	188(23.65)	305(20.57)	20(3.85)
20-49.99	150(21.87)	72(9.06)	222(14.97)	4(.77)
50-99.99	128(18.66)	0(0)	128(8.63)	1(.19)
≥ 100	172(25.07)	0(0)	172(11.60)	0(0)
Missing	5(.73)	7(.88)	14(.94)	0(0)
T-stage				
T0	1(.13)	4(.5)	5(.34)	NA
T1	83(10.44)	470(59.12)	553(37.29)	NA
T2	138(17.36)	316(39.75)	454(30.61)	NA
T3	399(50.19)	0(0)	399(26.90)	NA
T4	58(7.30)	0(0)	58(3.91)	NA
TX	7(.88)	5(.63)	14(.94)	NA
N-stage				
N0	130(16.35)	123(15.47)	253(17.06)	NA
N1	45(5.66)	0(0)	45(3.03)	NA
NX	511(64.28)	672(84.53)	1185(79.90)	NA
M-stage				
M0	324(47.23)	298(37.48)	622(41.94)	NA
M1	159(23.18)	0(0)	159(10.72)	NA
MX	203(29.59)	497(62.52)	702(47.34)	NA
Gleason (biopsy)				
≤ 4	7(1.02)	0(0)	7(.47)	NA
5	25(3.64)	1(.13)	26(1.75)	NA
6	86(12.54)	791(99.50)	877(59.14)	NA
7	218(31.78)	1(.13)	219(14.77)	NA
8	156(22.74)	0(0)	156(10.52)	NA
9	108(15.74)	0(0)	108(7.28)	NA
10	13(1.90)	0(0)	13(.88)	NA
Missing	73(10.64)	2(.25)	77(5.19)	NA

Supplementary Table 2. Clinical and demographic characteristics of subjects in JHH

Characteristics	# (%) of cases All cases (N=1,964)
Age at diagnosis (Year)	
Mean (sd)	57.75 (6.81)
Missing	9
Age at diagnosis (Year)	
≤ 65	1704 (87.16)
> 65	251 (12.84)
PSA levels at diagnosis (ng/ml)	
≤ 4	310 (16.28)
4.01-9.99	1220 (64.08)
10-19.99	256 (13.45)
20-49.99	66 (3.47)
50-99.99	23 (1.21)
≥ 100	29 (1.52)
Missing	60
T-stage	
T2	1247 (63.49)
T3a	454 (23.12)
T3b	105 (5.35)
T3c	12 (0.61)
T3X	7 (0.36)
T4	1 (0.05)
Missing	138 (7.03)
N-stage	
N0	1782 (97.38)
N1	37 (2.02)
N2	1 (0.05)
NX	10 (0.55)
M-stage	
M0	NA
M1	NA
MX	1828
Gleason (biopsy)	
≤ 4	0
5	41 (2.13)
6	1118 (58.17)
7(3+4 or unspecific)	474 (24.66)
7(4+3)	133 (6.92)
8	76 (3.95)
9	74 (3.85)
10	6 (0.31)
Missing	42

Supplementary Table 3. Inflation factor for the meta-analysis for 32 SNPs.

SNP1	N Obs	Median_p	Median_chisq	Inflation Factor
rs10086908	1117528	0.50	0.46	1.02
rs10486567	1117530	0.50	0.45	0.99
rs10896449	1117520	0.50	0.46	1.00
rs10934853	1117529	0.49	0.47	1.03
rs10993994	1117531	0.50	0.46	1.02
rs11649743	1117531	0.50	0.46	1.00
rs12418451	1117531	0.50	0.46	1.00
rs12621278	1117530	0.50	0.45	0.98
rs1447295	1117526	0.50	0.46	1.01
rs1465618	1117531	0.50	0.46	1.01
rs1512268	1117525	0.50	0.45	1.00
rs1571801	1117531	0.50	0.46	1.02
rs16901979	1117504	0.51	0.44	0.97
rs17021918	1117529	0.50	0.46	1.00
rs1859962	1117526	0.50	0.45	0.98
rs2660753	1117527	0.50	0.45	1.00
rs2735839	1117530	0.50	0.46	1.01
rs2928679	1117528	0.50	0.46	1.00
rs4430796	1117531	0.50	0.45	0.98
rs445114	1117531	0.50	0.46	1.01
rs4962416	1117530	0.50	0.47	1.02
rs5759167	1117531	0.50	0.46	1.01
rs5945619	1117527	0.50	0.45	1.00
rs6465657	1117522	0.50	0.46	1.02
rs6983267	1117530	0.50	0.46	1.01
rs7127900	1117531	0.50	0.46	1.01
rs721048	1117531	0.49	0.47	1.03
rs7679673	1117531	0.50	0.46	1.01
rs8102476	1117531	0.50	0.45	0.99
rs887391	1117530	0.50	0.46	1.01
rs9364554	1117531	0.50	0.45	0.99
rs9623117	1117531	0.50	0.45	0.98

Supplementary Table 4. Results for top SNPs that interact with the known PCa-risk SNPs (p<1.0E-05 in meta-analysis)

SNP 1			SNP 2							Meta-results		CAPS		JHH		CGEMS	
CHR	SNP	Gene	CHR	SNP	Position	Minor Allele	Gene	Location	Relative Position	P	OR	P	OR	P	OR	P	OR
2	rs12621278	*ITGA6*	3	rs1002979	113980570	C	*CD200R1L*	Intergenic	36676	3.10E-06	0.63(0.52-0.76)	1.45E-01	0.72(0.46-1.12)	2.66E-04	0.61(0.46-0.79)	9.29E-03	0.62(0.43-0.89)
2	rs12621278		8	rs1402649	20900514	G	*LOC286114*	Intergenic	3604	7.16E-06	1.58(1.29-1.92)	2.13E-01	1.33(0.85-2.10)	8.86E-05	1.74(1.32-2.29)	3.71E-02	1.48(1.02-2.14)
2	rs1465618	*THADA*	4	rs11735008	393303	G	*ABCA11P*	Intergenic	15921	6.65E-06	0.76(0.68-0.86)	5.04E-03	0.69(0.54-0.90)	3.11E-02	0.83(0.71-0.98)	1.35E-03	0.69(0.55-0.86)
2	rs1465618		13	rs9567349	43535405	G	*NCRNA00284*	Intergenic	32806	3.93E-06	0.61(0.49-0.75)	4.57E-04	0.41(0.25-0.67)	3.24E-02	0.72(0.54-0.97)	3.97E-03	0.57(0.39-0.84)
2	rs721048	*EHBP1*	1	rs3820259	239046585	C	*RGS7*	Intron		9.54E-06	1.39(1.20-1.60)	4.40E-02	1.45(1.01-2.08)	9.81E-05	1.46(1.21-1.76)	1.95E-01	1.20(0.91-1.59)
2	rs721048		6	rs9348131	166770788	T	*RPS6KA2*	Intron		6.11E-06	0.70(0.60-0.82)	2.45E-01	0.81(0.57-1.15)	6.83E-04	0.70(0.57-0.86)	3.19E-03	0.63(0.47-0.86)
2	rs721048		7	rs7809487	37110591	A	*ELMO1*	Intron		6.05E-06	0.72(0.62-0.83)	2.65E-01	0.82(0.58-1.16)	1.35E-04	0.69(0.57-0.83)	2.03E-02	0.72(0.55-0.95)
2	rs721048		13	rs9546364	82850742	T	*SLITRK1*	Intergenic	498602	6.33E-06	0.64(0.53-0.78)	6.88E-04	0.48(0.31-0.73)	2.75E-05	0.56(0.43-0.74)	9.45E-01	1.01(0.70-1.46)
3	rs10934853	*EEFSEC*	9	rs7847271	116870633	A	*TNC*	Intron		3.85E-06	0.67(0.56-0.79)	7.73E-03	0.60(0.41-0.87)	2.56E-03	0.68(0.54-0.88)	1.87E-02	0.69(0.50-0.94)
3	rs10934853		14	rs12433148	45666182	A	*RPL10L*	Intergenic	523788	9.25E-06	1.33(1.17-1.50)	6.91E-03	1.48(1.11-1.96)	4.50E-05	1.43(1.20-1.69)	6.32E-01	1.06(0.83-1.35)
3	rs10934853		14	rs2400997	100796860	T	*MIR656*	Intergenic	193969	2.51E-06	1.25(1.14-1.38)	4.80E-05	1.57(1.26-1.95)	6.76E-02	1.13(0.99-1.28)	1.95E-03	1.34(1.11-1.60)
3	rs10934853		18	rs998124	40979660	G	*MIR4319*	Intergenic	-175531	5.21E-06	1.33(1.18-1.51)	3.56E-02	1.39(1.02-1.88)	3.64E-03	1.28(1.08-1.51)	3.56E-03	1.42(1.12-1.80)
3	rs2660753	*NA*	5	rs7717572	66869013	A	*CD180*	Intergenic	-340640	3.39E-06	1.94(1.47-2.56)	2.84E-01	1.60(0.68-3.78)	2.80E-05	2.12(1.49-3.02)	5.80E-02	1.69(0.98-2.89)
3	rs2660753		6	rs319097	107852552	C	*PDSS2*	Intron		9.59E-06	1.35(1.18-1.54)	2.02E-01	1.27(0.88-1.85)	3.15E-06	1.49(1.26-1.76)	5.53E-01	1.08(0.83-1.41)
3	rs2660753		13	rs7139820	106284593	A	*ARGLU1*	Intergenic	-266078	5.64E-06	0.56(0.44-0.72)	1.47E-02	0.46(0.25-0.86)	2.07E-05	0.49(0.35-0.68)	4.97E-01	0.85(0.53-1.36)
4	rs17021918	*PDLIM5*	3	rs9757252	86977168	T	*VGLL3*	Intergenic	92645	4.73E-06	1.25(1.13-1.37)	8.45E-03	1.35(1.08-1.69)	2.23E-03	1.22(1.07-1.38)	2.16E-02	1.24(1.03-1.50)
4	rs17021918		8	rs2921007	8269681	A	*SGK223*	Intron		6.10E-06	1.40(1.21-1.63)	1.79E-02	1.60(1.08-2.35)	3.59E-06	1.58(1.30-1.92)	8.40E-01	1.03(0.78-1.36)
4	rs7679673	*TET2*	9	rs290258	92595560	G	*SYK*	Intergenic	-8273	1.49E-06	0.75(0.67-0.84)	2.11E-03	0.66(0.51-0.86)	3.01E-03	0.78(0.67-0.92)	1.39E-02	0.75(0.59-0.94)
4	rs7679673		11	rs11605083	15311822	C	*INSC*	Intergenic	86492	4.42E-06	1.28(1.15-1.43)	3.28E-01	1.13(0.89-1.44)	8.20E-04	1.28(1.11-1.48)	9.71E-04	1.42(1.15-1.75)
4	rs7679673		22	rs5751168	21175240	T	*ZNF280B*	Intron		4.11E-06	1.44(1.23-1.67)	4.75E-05	2.19(1.50-3.19)	3.38E-02	1.25(1.02-1.53)	9.09E-03	1.48(1.10-1.99)
6	rs9364554	*NA*	6	rs9351730	69351206	A	*BAI3*	Intergenic	-51147	4.98E-06	1.25(1.13-1.37)	6.97E-02	1.22(0.98-1.52)	1.01E-03	1.25(1.09-1.42)	8.99E-03	1.27(1.06-1.52)
7	rs10486567	*JAZF1*	3	rs1795355	41574530	T	*ULK4*	Intron		9.46E-06	0.79(0.71-0.88)	3.37E-02	0.77(0.60-0.98)	9.11E-03	0.83(0.72-0.95)	2.14E-03	0.73(0.60-0.89)
7	rs10486567		3	rs11720607	174325971	G	*SPATA16*	Intron		4.87E-06	0.73(0.63-0.83)	2.45E-03	0.62(0.45-0.84)	2.34E-03	0.75(0.62-0.90)	5.43E-02	0.77(0.58-1.00)
7	rs6465657	*LMTK2*	3	rs12485321	124986	A	*CHL1*	Intergenic	-88664	2.66E-06	0.81(0.74-0.88)	7.36E-02	0.83(0.67-1.02)	2.89E-05	0.78(0.69-0.88)	1.09E-01	0.87(0.74-1.03)
7	rs6465657		3	rs6548941	66555095	T				7.23E-06	1.32(1.17-1.49)	8.73E-03	1.49(1.11-2.01)	2.60E-05	1.42(1.21-1.67)	6.02E-01	1.06(0.84-1.34)
7	rs6465657		16	rs8057939	47951777	C	*C16orf78*	Intergenic	-13532	4.71E-06	1.37(1.20-1.57)	3.31E-02	1.43(1.03-1.98)	1.03E-03	1.36(1.13-1.63)	1.70E-02	1.36(1.06-1.75)

Supplementary Table 4 cont'd

SNP 1			SNP 2							Meta-results		CAPS		JHH		CGEMS	
CHR	SNP	Gene	CHR	SNP	Position	Minor Allele	Gene	Location	Relative Position	P	OR	P	OR	P	OR	P	OR
8	rs10086908	*NA*	4	rs7694725	114220405	T	*ANK2*	Intron		1.55E-06	1.36(1.20-1.55)	7.99E-03	1.46(1.10-1.92)	1.41E-05	1.47(1.24-1.75)	3.89E-01	1.11(0.87-1.42)
8	rs10086908		6	rs10456809	17921804	T	*KIF13A*	Intron		4.83E-06	1.25(1.14-1.38)	1.30E-02	1.31(1.06-1.62)	2.28E-03	1.23(1.08-1.40)	1.69E-02	1.26(1.04-1.52)
8	rs10086908		10	rs4917911	102549411	G	*PAX2*	Intron		7.70E-06	1.43(1.22-1.67)	3.40E-02	1.46(1.03-2.07)	2.63E-04	1.48(1.20-1.83)	1.03E-01	1.30(0.95-1.79)
8	rs1447295	*NA*	7	rs7789197	40931652	A	*INHBA*	Intergenic	763474	3.36E-06	0.66(0.56-0.79)	2.57E-03	0.55(0.38-0.81)	7.27E-03	0.72(0.56-0.91)	1.06E-02	0.66(0.48-0.91)
8	rs1447295		9	rs12682851	8002418	G	*C9orf123*	Intergenic	-212619	1.53E-06	0.72(0.63-0.82)	9.66E-03	0.67(0.50-0.91)	2.15E-03	0.75(0.62-0.90)	6.56E-03	0.70(0.54-0.90)
8	rs1447295		10	rs10885582	116317540	T	*ABLIM1*	Intron		3.70E-06	0.73(0.63-0.83)	9.33E-05	0.54(0.39-0.73)	1.27E-02	0.79(0.66-0.95)	3.46E-02	0.75(0.57-0.98)
8	rs1447295		15	rs11637980	94803657	G	*NR2F2*	Intergenic	119161	1.55E-06	0.68(0.58-0.79)	1.67E-03	0.58(0.41-0.82)	5.73E-02	0.81(0.65-1.01)	8.29E-05	0.52(0.38-0.72)
8	rs1512268	*NKX3.1*	6	rs2523395	29810489	A	*LOC285830*	Intron		1.53E-06	1.24(1.14-1.35)	1.89E-01	1.14(0.94-1.39)	4.54E-02	1.13(1.00-1.26)	2.98E-08	1.65(1.38-1.97)
8	rs1512268		7	rs517761	103156254	T	*RELN*	Intron		6.93E-06	0.82(0.75-0.90)	1.46E-01	0.86(0.70-1.05)	2.46E-05	0.78(0.70-0.88)	1.64E-01	0.89(0.75-1.05)
8	rs1512268		13	rs16944141	89663547	A	*MIR622*	Intergenic	-17890	2.98E-06	0.65(0.54-0.78)	1.54E-01	0.76(0.51-1.11)	7.73E-07	0.54(0.42-0.69)	4.43E-01	0.87(0.60-1.25)
8	rs16901979	*NA*	12	rs12317459	81688687	A	*TMTC2*	Intron		3.80E-06	2.06(1.52-2.80)	7.13E-02	1.92(0.94-3.91)	1.71E-04	2.21(1.46-3.33)	4.00E-02	1.88(1.03-3.42)
8	rs2928679	*NKX3.1*	2	rs17198717	181943741	C	*ITGA4*	Intergenic	-86123	7.80E-06	0.80(0.72-0.88)	3.19E-01	0.89(0.70-1.12)	2.91E-05	0.75(0.65-0.86)	6.73E-02	0.84(0.69-1.01)
8	rs445114	*NA*	22	rs6005451	26182183	C	*MN1*	Intergenic	292082	4.10E-06	1.42(1.22-1.65)	4.95E-01	1.13(0.79-1.63)	1.71E-04	1.46(1.20-1.77)	3.28E-03	1.58(1.16-2.14)
8	rs6983267	*NA*	6	rs1011119	19972144	G	*ID4*	Intergenic	23250	7.20E-06	0.81(0.74-0.89)	1.45E-02	0.76(0.61-0.95)	2.85E-03	0.83(0.74-0.94)	1.58E-02	0.80(0.67-0.96)
8	rs6983267		15	rs543686	32855601	T	*ACTC1*	Intergenic	11988	4.02E-06	1.24(1.13-1.35)	1.37E-01	1.18(0.95-1.45)	1.50E-04	1.26(1.12-1.42)	2.52E-02	1.22(1.03-1.46)
9	rs1571801	*DAB2IC*	8	rs2219968	79119213	A	*PKIA*	Intergenic	-471678	6.07E-07	1.30(1.17-1.43)	1.18E-02	1.35(1.07-1.70)	1.64E-04	1.30(1.14-1.50)	3.17E-02	1.24(1.02-1.52)
9	rs1571801		8	rs13264970	83236384	C	*SNX16*	Intergenic	-319308	3.53E-06	0.77(0.69-0.86)	1.50E-02	0.74(0.59-0.94)	5.02E-03	0.80(0.68-0.93)	3.92E-03	0.72(0.58-0.90)
9	rs1571801		10	rs1547851	92364806	T	*HTR7*	Intergenic	125750	7.45E-06	1.59(1.30-1.95)	2.72E-03	1.98(1.27-3.09)	7.35E-03	1.49(1.11-1.99)	2.42E-02	1.52(1.06-2.20)
9	rs1571801		21	rs11702869	19512402	A	*TMPRSS15*	Intergenic	-814561	8.54E-06	0.79(0.71-0.87)	1.11E-01	0.83(0.66-1.04)	4.50E-05	0.74(0.64-0.85)	1.44E-01	0.86(0.70-1.05)
10	rs10993994	*MSMB*	3	rs6766510	12526807	C	*TSEN2*	Intron		1.77E-06	1.58(1.31-1.91)	9.37E-02	1.46(0.94-2.26)	2.98E-05	1.75(1.34-2.27)	5.32E-02	1.41(1.00-1.98)
10	rs10993994		4	rs567404	16810346	G	*QDPR*	Intergenic	286768	5.91E-06	0.81(0.74-0.89)	7.30E-02	0.82(0.66-1.02)	1.16E-04	0.78(0.69-0.89)	7.90E-02	0.85(0.71-1.02)
10	rs4962416	*CTBP2*	5	rs10940579	57166575	C	*ACTBL2*	Intergenic	-352182	3.81E-06	1.32(1.18-1.49)	4.85E-02	1.36(1.00-1.84)	1.77E-03	1.29(1.10-1.51)	4.74E-03	1.39(1.10-1.74)
10	rs4962416		7	rs9649213	97859147	G	*BAIAP2L1*	Intron		1.42E-06	1.28(1.16-1.42)	7.77E-01	1.04(0.80-1.34)	6.18E-06	1.36(1.19-1.55)	1.40E-02	1.27(1.05-1.54)
10	rs4962416		9	rs10810120	14234376	C	*NFIB*	Intron		8.44E-06	1.40(1.21-1.62)	6.39E-02	1.39(0.98-1.96)	5.58E-03	1.32(1.08-1.61)	1.76E-03	1.59(1.19-2.12)
11	rs10896449	*MYEOV*	2	rs13398206	198877341	C	*PLCL1*	Intergenic	154488	3.67E-06	1.24(1.13-1.36)	6.86E-01	1.05(0.84-1.30)	1.29E-04	1.27(1.12-1.44)	1.91E-03	1.33(1.11-1.58)
11	rs10896449		7	rs6968681	130286690	T	*FLJ43663*	Intron		7.31E-06	0.79(0.72-0.88)	5.86E-01	0.94(0.76-1.17)	4.78E-05	0.75(0.65-0.86)	1.14E-02	0.78(0.64-0.95)
11	rs10896449		12	rs17354197	88169501	T	*DUSP6*	Intergenic	96467	8.82E-06	1.41(1.21-1.64)	3.97E-02	1.49(1.02-2.18)	2.35E-03	1.37(1.12-1.67)	1.10E-02	1.45(1.09-1.92)
11	rs10896449		21	rs447988	39410617	T	*PSMG1*	Intergenic	58637	5.79E-06	0.67(0.56-0.80)	1.96E-01	0.76(0.50-1.15)	1.93E-02	0.76(0.60-0.96)	1.73E-05	0.49(0.35-0.68)

Supplementary Table 4 cont'd

SNP 1			SNP 2							Meta-results		CAPS		JHH		CGEMS	
CHR	SNP	Gene	CHR	SNP	Position	Minor Allele	Gene	Location	Relative Position	P	OR	P	OR	P	OR	P	OR
11	rs12418451	*MYEOV*	3	rs1916284	57369806	C	*DNAH12*	Intron		1.31E-06	0.79(0.71-0.87)	1.12E-01	0.83(0.65-1.05)	2.69E-05	0.76(0.66-0.86)	4.50E-02	0.83(0.68-1.00)
11	rs12418451		3	rs10513723	176062702	A	*NAALADL2*	Intron		5.61E-06	1.41(1.21-1.63)	7.22E-03	1.58(1.13-2.21)	1.61E-02	1.27(1.05-1.54)	1.46E-03	1.64(1.21-2.22)
11	rs12418451		8	rs7829048	4689690	C	*CSMD1*	Intron		9.76E-06	0.74(0.65-0.85)	1.22E-02	0.68(0.50-0.92)	4.52E-02	0.84(0.71-1.00)	1.81E-04	0.60(0.46-0.78)
11	rs12418451		14	rs1243647	20094459	A	*RNASE9*	missense	TCG)204P(CCG)	1.42E-06	0.75(0.67-0.84)	6.63E-02	0.77(0.58-1.02)	5.02E-04	0.76(0.65-0.88)	4.91E-03	0.72(0.58-0.91)
11	rs12418451		15	rs784411	46827089	C	*CEP152*	Intron		1.15E-07	1.42(1.25-1.61)	8.83E-03	1.55(1.12-2.16)	5.28E-04	1.34(1.14-1.58)	1.32E-03	1.53(1.18-1.99)
11	rs7127900	*IGF2, IGF2AS*	2	rs3789080	111514002	C	*ACOXL*	Intron		4.37E-06	0.71(0.61-0.82)	2.23E-02	0.69(0.51-0.95)	1.24E-04	0.67(0.54-0.82)	1.32E-01	0.80(0.61-1.07)
11	rs7127900	*INS,TH*	8	rs13258681	124783903	C	*ANXA13*	Intron		3.65E-06	1.32(1.17-1.48)	4.58E-02	1.32(1.01-1.73)	5.43E-04	1.33(1.13-1.56)	1.90E-02	1.31(1.05-1.64)
11	rs7127900		13	rs9594759	41930593	C	*TNFSF11*	Intergenic	-104279	7.96E-06	0.78(0.70-0.87)	3.34E-01	0.88(0.69-1.14)	4.58E-04	0.77(0.67-0.89)	4.43E-03	0.73(0.58-0.91)
11	rs7127900		22	rs12628051	38984222	C	*TNRC6B*	Intron		3.39E-06	1.30(1.17-1.46)	1.82E-03	1.50(1.16-1.93)	6.14E-03	1.24(1.06-1.44)	1.44E-02	1.32(1.06-1.65)
11	rs7127900		22	rs4821941	39005037	G	*TNRC6B*	Intron		4.35E-06	1.30(1.16-1.46)	2.71E-03	1.48(1.15-1.91)	6.61E-03	1.23(1.06-1.44)	1.27E-02	1.33(1.06-1.66)
17	rs11649743	*HNF1B*	6	rs13192613	123324640	T	*CLVS2*	Intergenic	-34641	3.07E-06	1.37(1.20-1.56)	6.67E-03	1.56(1.13-2.16)	3.69E-04	1.38(1.16-1.65)	8.49E-02	1.24(0.97-1.59)
17	rs4430796	*HNF1B*	1	rs731174	37969428	C	*EPHA10*	Intron		4.55E-06	1.27(1.15-1.40)	5.03E-02	1.24(1.00-1.54)	3.20E-02	1.18(1.01-1.38)	1.13E-04	1.41(1.19-1.68)
17	rs4430796		2	rs12694942	158518681	T	*UPP2*	Intergenic	-41256	7.84E-06	0.80(0.73-0.88)	5.22E-03	0.75(0.61-0.92)	1.87E-03	0.79(0.68-0.92)	6.36E-02	0.85(0.72-1.01)
17	rs4430796		3	rs13067734	143445705	C	*GK5*	Intergenic	-18566	8.07E-06	0.80(0.73-0.88)	3.87E-01	0.91(0.74-1.13)	8.47E-02	0.88(0.77-1.02)	2.79E-07	0.63(0.53-0.75)
17	rs4430796		9	rs10812303	25712117	T	*TUSC1*	Intergenic	-43261	5.59E-06	1.34(1.18-1.52)	6.63E-03	1.46(1.11-1.91)	7.57E-03	1.27(1.07-1.52)	9.01E-03	1.37(1.08-1.73)
17	rs4430796		9	rs7855134	70264671	T	*PGM5*	Intron		7.52E-06	1.76(1.38-2.26)	3.79E-02	1.89(1.04-3.44)	1.92E-04	1.93(1.37-2.73)	9.14E-02	1.46(0.94-2.28)
17	rs4430796		12	rs4489787	47097367	C	*ANP32D*	Intergenic	-55348	1.26E-06	0.68(0.58-0.80)	5.26E-01	0.89(0.63-1.27)	1.41E-03	0.70(0.56-0.87)	3.05E-05	0.55(0.42-0.73)
17	rs1859962	*NA*	2	rs16867225	180749531	A	*CWC22*	Intergenic	-169506	3.12E-06	0.64(0.53-0.77)	1.33E-03	0.48(0.30-0.75)	4.80E-03	0.70(0.54-0.90)	1.84E-02	0.65(0.45-0.93)
17	rs1859962		7	rs10277209	108790810	C	*C7orf66*	Intergenic	-478937	3.81E-06	1.36(1.19-1.55)	4.08E-02	1.39(1.01-1.89)	4.04E-03	1.29(1.08-1.53)	1.55E-03	1.52(1.17-1.97)
19	rs2735839	*KLK3*	20	rs6089829	61139481	A	*LOC63930*	Intron		3.21E-06	0.74(0.65-0.84)	2.53E-02	0.71(0.52-0.96)	1.26E-03	0.75(0.64-0.90)	1.10E-02	0.72(0.56-0.93)
19	rs8102476	*NA*	1	rs1866967	29958249	G	*PTPRU*	Intergenic	432337	5.16E-06	0.82(0.75-0.89)	2.70E-02	0.79(0.64-0.97)	5.10E-03	0.85(0.75-0.95)	2.97E-03	0.78(0.66-0.92)
19	rs8102476		10	rs10795917	12091822	G	*UPF2*	Intron		6.79E-07	1.24(1.14-1.36)	1.88E-01	1.15(0.93-1.41)	1.13E-04	1.26(1.12-1.42)	3.14E-03	1.27(1.08-1.50)
19	rs887391	*PPP1R14A*	4	rs735172	5809770	C	*EVC*	Intron		2.03E-06	1.31(1.17-1.46)	6.58E-03	1.43(1.10-1.85)	2.37E-03	1.27(1.09-1.47)	1.02E-02	1.32(1.07-1.63)
19	rs887391		5	rs4463179	13558432	A	*DNAH5*	Intergenic	185005	2.22E-06	0.64(0.53-0.77)	3.00E-02	0.64(0.42-0.96)	8.35E-05	0.59(0.46-0.77)	8.28E-02	0.73(0.51-1.04)
19	rs887391		8	rs2981156	39988790	C	*IDO2*	Intron		8.07E-06	1.31(1.16-1.47)	2.22E-03	1.53(1.17-2.02)	1.06E-03	1.31(1.11-1.53)	1.58E-01	1.18(0.94-1.47)
19	rs887391		12	rs10844540	33349548	A	*SYT10*	Intergenic	70067	7.59E-06	1.40(1.21-1.62)	3.86E-02	1.43(1.02-2.02)	8.40E-02	1.19(0.98-1.45)	6.16E-06	1.96(1.46-2.62)
22	rs5759167	*TTLL1,BIK,*	7	rs12111744	20988023	A	*RPL23P8*	Intergenic	154059	5.95E-06	1.30(1.16-1.46)	3.33E-01	1.14(0.88-1.48)	5.44E-04	1.31(1.12-1.53)	2.50E-03	1.42(1.13-1.78)
22	rs5759167	*MCAT,PACSIN2*	12	rs2711721	45658537	T	*AMIGO2*	Intergenic	97220	2.11E-06	1.28(1.16-1.42)	1.90E-01	1.22(0.91-1.65)	1.75E-04	1.29(1.13-1.47)	9.06E-03	1.30(1.07-1.58)
22	rs5945619	*NUDT10*	7	rs7792744	97325907	C	*ASNS*	Intron		5.62E-06	0.80(0.73-0.88)	9.09E-05	0.74(0.64-0.86)	1.00E+00	1.00(1.00-1.00)	7.82E-03	0.85(0.75-0.96)
22	rs5945619		9	rs1044214	85465379	A	*UBQLN1*	utr3		7.97E-06	1.26(1.14-1.39)	5.88E-04	1.32(1.13-1.55)	1.00E+00	1.00(1.00-1.00)	3.05E-03	1.22(1.07-1.39)
22	rs5945619		18	rs6507016	29181773	T	*C18orf34*	Intron		4.33E-06	0.78(0.71-0.87)	2.54E-02	0.83(0.70-0.98)	1.00E+00	1.00(1.00-1.00)	4.10E-05	0.76(0.66-0.86)
22	rs9623117	*TNRC6B*	3	rs6763848	1487587	A	*CNTN6*	Intergenic	67309	3.90E-06	1.30(1.16-1.45)	7.99E-01	1.03(0.80-1.34)	1.27E-06	1.44(1.24-1.66)	8.57E-02	1.21(0.97-1.51)
22	rs9623117		4	rs1713511	43472127	A	*KCTD8*	Intergenic	398550	7.87E-06	1.31(1.16-1.47)	4.94E-03	1.54(1.14-2.09)	6.71E-03	1.23(1.06-1.44)	1.06E-02	1.36(1.07-1.72)
22	rs9623117		6	rs2844806	30041418	T	*HCG9*	Intergenic	-9453	8.12E-06	1.27(1.14-1.41)	1.82E-01	1.20(0.92-1.55)	3.45E-03	1.23(1.07-1.41)	7.92E-04	1.43(1.16-1.76)
22	rs9623117		6	rs1200562	70960267	C	*COL19A1*	Intron		9.96E-06	0.64(0.53-0.78)	1.33E-01	0.71(0.46-1.11)	8.29E-06	0.54(0.42-0.71)	3.62E-01	0.83(0.57-1.23)

Abbreviations: SNP1 indicate the 32 known PCa-risk SNPs. SNP 2 indicates the interacting SNPs; Chr, chromosome; Relative position is the distance of SNP2 relative to the nearest gene if SNP2 is located in the intergenic region; OR : Odds Ratio; P and OR are for the multiplicative interaction term. P and OR for the Meta-analysis are calculated based on a Cochran-Mantel-Haenszel test. CAPS: PCa case-control study from Sweden; JHH: Johns Hopkins Hospital; CGEMS: the Cancer Genetic Markers of Susceptibility;